REMARKS

The Obviousness-type Double Patenting Rejection

Claims 14-18, 48, 54-65, 106-108, and 118-130 were rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-53 of US Patent 6,642,363 in view of claims 1-35 of US Patent 6,797,738, claims 1-36 of US Patent 6,281,256, claims 1-77 of US Patent 5,763,416 and claims 1-130 of US Patent 5,942,496. For reasons discussed below, the applicants request that the examiner clarify this rejection with specificity.

Claims 1-53 of US Patent 6,642,363 ["the '363 patent"] relate generally to a modified alginate (and compositions and methods for use thereof) comprising at least one alginate chain covalently bonded to at least one cell attachment peptide or RGD peptide that promotes cell adhesion or growth. See, e.g., claim 1. The '363 patent arose from USSN 09/147,900 filed 5-3-1999, claiming priority of PCT/US97/16890 filed 9-19-1997, which claims priority of three provisional applications: USSN 60/041,565 filed 3-21-97, USSN 60/026,362 filed 9-19-96, and USSN 60/026,467 filed 9-19-96. The 20 year term of the '363 patent is measured from the 9-9-97 PCT application filing date.

Claims 1-35 of US Patent 6,797,738 ["the '738 patent"] relate to methods for preparing (and methods of use for) a porous biocompatible polymer. The '738 patent arose from USSN 09/939,714 filed 8-28-01 claiming priority of USSN 09/402,119 filed 6-6-00 and USSN 60/042,198 filed 3-31-97. This priority claim was obtained from the USPTO website and appears to be incomplete, as the application is in the family of applications which gave rise to US Patent 6,281,256 discussed below. The 20 year patent term is therefore presumed to be measured from the 3-31-98 PCT application filing date.

Claims 1-36 of US Patent 6,281,256 ['the 256 patent"] relate to methods for preparing (and methods of use for) a porous polymer material comprising specific polymeric

components. The '256 patent arose from USSN 09/402,119 filed 6-6-00, claiming priority of PCT/US98/06188 filed 3-31-98 and USSN 60/042,198 filed 3-31-1997. The 20 year term of the '256 patent is measured from the PCT application filing date of 3-31-98.

Claims 1-77 of US Patent 5,763,416 ["the '416 patent"] relate generally to methods for transferring a nucleic acid into bone progenitor cells and expressing a protein encoded by the nucleic acid in said cells. The '416 patent arose from USSN 08/199,780 filed 2-18-94 and the pre-GATT 17 year term of the patent is measured from its issue date of 6-9-98.

Claims 1-130 of US Patent 5,942,496 ["the '496 patent"] relate generally to methods for transferring two or more nucleic acid segments into bone progenitor cells and expressing products encoded by said nucleic acid segments. The '496 patent arose from USSN 08/316,650 filed 9-30-94, claiming priority of USSN 08/199,780 filed 2-18-94. The pre-GATT 17 year term of the '496 patent is measured from its issue date of 8-24-99.

None of the claims in the '416 patent, the '496 patent, the '738 patent or the '256 patent recite an alginate matrix expressly claimed in the instant application. Accordingly, the claims of these patents, alone or in combination, cannot render obvious the subject matter of the instant application.

Only claims in the '363 patent set forth an alginate product. As noted above, the '363 patent claims benefit of an earlier-filed PCT application in addition to three US provisional application. Accordingly, to the extent the examiner is able to establish a *prima facie* case for obviousness-type double patenting, and the applicants do not admit that the examiner has properly supported the rejection, clarification is requested as to how much term the applicants are requested to disclaim should a terminal disclaimer be filed.

The §103 Rejection

The examiner rejected claims 14, 17, 18, 48, 106-108, 118-130 under 35 USC §103(a) for being directed to subject matter assertedly rendered obvious by the disclosure of Shapiro, et al., Biomaterials 18:583 (1997) ["Shapiro"] in view of the disclosures of Fang, et al., Proc. Natl. Acad. Sci. 93:5753 (1996) [incorrectly cited in the Office Action as 03:5773, "Fang"] and Kawada, et al., FEBS Letts. 408:43 (1997) ['Kawada"].

Shapiro was cited for disclosing porous alginate sponges for cell culture and transplantation. [Action, p. 5] The examiner admitted that Shapiro "does not teach incorporation of nucleic acid molecule in the matrix and that the matrix is capable of mediating cellular interaction via alginate chain section." [Action, p. 5] It is unclear what the examiner meant by the phrase "mediating cellular interaction via alginate chain section."

Fang was cited for disclosing (i) gene-activated matrices (GAMs) comprising a biodegradable matrix (collagen sponges) containing nucleic acid molecules, (ii) transplantation of the GAMs in an animal model and expression of "a maker gene, PTH-34, BMP-4 or TGF-β genes in host animals, and (iii) implantation of porous matrices resulting in genetic modification of host cells and expression of a gene product of interest. [Action, p. 5] The examiner did not admit to any deficiencies in the disclosure of Fang.

Kawada was cited for disclosing that "alginate contains mixture of oligosaccharides that are capable of mediating cellular interaction." [Action, p. 6]

From the combination of this disclosure, the examiner concluded that it would have been obvious to one of ordinary skill in the art to modify the alginate sponge disclosed in Shapiro to incorporate nucleic acids as taught by Fang. The examiner added,

> One would have been motivated to do so to induce gene expression of interest in host cells at the site of sponge transplantation. One would have a reasonable expectation of success in doing so, since genetic modification of host cells by transplanting a porous matrix has been routine in the art at the time the instant invention was made. In addition, given the

> scope of a molecule that mediates a cellular interaction the alginate matrix inherently contains alginate chains section bonded to various oligosaccharides that mediate cellular interaction (see Kawada). Thus the invention as claimed is *prima facie* obvious in view of the cited prior art of record.

[Action, p. 6]

The applicants respectfully disagree. The examiner's position rests on the assumption that the worker of ordinary skill would have been motivated to substitute the biodegradable collagen matrix described in Fang with the alginate sponge described in Shapiro, yet nothing in the Action or the cited references suggests such a modification should be effected or why such a modification would be desirable.

As discussed in Shapiro, alginate "refers to a family of polyanionic copolymers derived from brown sea algae...." [p. 583, second column] Alginate is therefore heterologous to all species except algae, and its use in for example, a mammal, can be expected to evoke at least some degree of an immune response. Indeed, Shapiro addresses this issue at p. 583, second column, last paragraph bridging to p. 584:

> Previous applications of alginates for cell transplantation have focused on systems where a semipermeable membrane, made of alginate-poly(L-lysine), was necessary to protect cells from the host immune system. [References omitted] This coating greatly reduces the microcapsule permeability toward nutrients, often leading to death of the encapsulated cells. In clinical applications, such a barrier may not be necessary since the immune-suppressive drugs which are currently successfully used for whole organ transplants could also be used for transplanted cells.

Whether Shapiro is addressing an immune response against the encapsulated cells, the alginate matrix, or both, is unclear. Regardless, the worker of ordinary skill would appreciate that use of a mammalian protein matrix, e.g., collagen as taught by Fang, in a mammal would offer advantages over an algae-derived matrix as described by Shapiro in that the human protein is considerably less likely to evoke an immune response.

Shapiro also discusses other unknown factors associated with using an alginate matrix. While acknowledging that "alginates are approved by several regulatory authorities, such as the Food and Drug Administration, for wound dressing and as food additives" [p. 583, second column], the authors note that the kinetics of alginate matrix degradation *in vivo* remains to be elucidated. After discussing at p. 588, second column, last paragraph, results from *in vitro* experiments, Shapiro states,

> Taken together, these results suggest that the sponges are suitable for the long-term *in vitro* culturing of cells. It still remains to examine their degradability. The goal is to achieve scaffolds which will maintain their template shape and dimensions while the tissue is regenerated, and be eliminated at a later stage.

While Shapiro adds, "Alginate hydrogels appear to fulfil [sic] this requirement" [*Id.*], one can only conclude that this statement is directed to the ability of alginate to maintain its shape rather characteristics of its elimination, since Shapiro admitted earlier that alginate degradation "remains to be elucidated." Shapiro expressly states as much in the "Conclusions" section at p. 589,

> Alginate is an ideal material for transplantation; it is biocompatible and hydrophilic. Furthermore, the alginate sponges developed herein appear to possess structural and morphological properties that are appropriate for cell growth and proliferation, and for neovascularization. At present, *in vivo* studies are directed toward characterizing the extent of neovascularization of the alginate sponges, their biocompatibility and degradation.

Thus, Shapiro raises more questions regarding the consequences of *in vivo* use of alginate matrices than it answers.

Given the unknowns discussed in Shapiro, the applicants submit that the worker of ordinary skill would not be motivated to substitute alginate for Fang's collagen matrix. Indeed, if, as the examiner purports, the desired result is to "induce gene expression of interest in host cells at the site of sponge transplantation" [Action, p. 6], such a result could

be obtained using the method described in Fang, which was in fact demonstrated to be effective in an *in vivo* model, without the need to assess any unforeseen consequences associated with using an alginate matrix. Accordingly, the applicants submit that the examiner has failed to establish a *prima facie* case of obviousness and the rejection of claims under section 103(a) must be withdrawn.

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